REMARKS

Claims 1, 2, 4, 5, 8, 9, 13, 14, 16, 17, 19, and 136 remain pending. The Examiner has acknowledged that claim 136 would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Claims 137-158 have been added. Claims 137-158 read on elected Species A): peptide. Claims 137-158 read on elected Species B): *E. coli*. Under 37 CFR 1.141, upon allowance of any generic claim, Applicant will be entitled to consideration of claims to additional non-elected species which are written in dependent form or otherwise include all the limitations of an allowed generic claim.

The amendment to the specification on page 35 harmonized this passage with the language of claim 1 and 13. Claim 1 provides that X_7 may be "Gly, an amide-substituted polar residue or a hydrophobic residue." Claim 13 recites that X_7 may be glycine, asparagine, or alanine. However, the specification in describing these embodiments listed glycine, *histidine*, or alanine. The specification defines histidine as a basic hydrophilic residue; histidine is neither "an amide-substituted polar residue or a hydrophobic residue" per claim 1, nor glycine, asparagine, or alanine per claim 13. As such, the specification has been amended to conform to the claims.

Claim 1 was amended to focus upon Formula I, and as such, the scope of the claim was not expanded. Further, claim 1 was amended to reflect one of the alternative features of dependent claim 13.

Claims 4 and 8 have been amended to replace "mimic" with "compound." Support for the amendments include:

> [C]ompounds that bind the G_1 beta-strand of a periplasmic chaperone [and/or] the amino-terminal end of a pilus subunit .... may be used as lead compounds in pharmaceutical efforts to identify **compounds that inhibit pilus biogenesis**....[1]
>
> In a preferred embodiment of the invention, the compounds are peptides or peptide analogs that mimic the binding

[1] Specification, p. 56, ln. 18 – 21 (emphasis added).

> activity of the G_1 beta-strand of a chaperone and that exhibit antibacterial activity against a Gram-negative bacterium.[2]

Claims 5 and 9 have been amended to make the spelling of analog consistent through the application. No change in scope or meaning is intended.

Claim 13 has been amended to depend from claim 1 due to cancellation of claim 12. Claim 14 finds support at page 32, lines 6-8 and the fact that claim 1 allows the mimic to be ten to twenty residues and the specific sequences listed in claim 14 are ten residues in length. Thus, various embodiments of the mimic of claim 14 include the ten residue sequences as listed and longer sequences comprising these listed sequences.

Claim 16 has been redrafted in independent form while the scope of the claim was not altered.

Claims 19 and 158 finds support in the Specification as follows:

> [C]ompounds that bind the G_1 beta-strand of a periplasmic chaperone [and/or] the amino-terminal end of a pilus subunit .... may be used as lead compounds in pharmaceutical efforts to identify compounds that inhibit pilus biogenesis as a therapeutic approach toward the treatment of several types of disease caused by pathogenic Gram-negative bacteria **such as** *Escherichia coli, Haemophilus influenzae, Salmonella enteriditis, Salmonella typhimurium, Bordetella pertussis, Yersinia enterocolitica, Yersinia perstis, Helicobacter pylori and Klebsiella pneumoniae*.[3]

This passage demonstrates that it was intended for such Gram-negative bacteria as those listed to serve as examples rather than a list requiring that an antibacterial compound demonstrate activity against each and every type. Of course, it is contemplated that various embodiments of the compound of the claims would exhibit antibacterial against all such Gram-negative bacteria; however, it is similarly contemplated that other embodiments would exhibit antibacterial activity against but one, two, or several of the Gram-negative bacteria listed.

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[2] Specification, p. 37, ln. 2-4.
[3] Specification, p. 56, ln. 19-24 (emphasis added).

Claim 136 was amended as an independent claim based upon the Office's suggestion that it would allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim 137-138 finds support in the specification at pages 35-37. Support for claim 139 appears on page 6, lines 24-26. Support for the complex of claims 140-155 is found on, for example, page 23, line 5. Support for the synthetic compound in the complex of claims 140-155 may be found in the specification on: page 31, line 20-page 32, line 5; page 21, line 11-page 22, line 7; and by sequences disclosed in Table 2 on pages 36-37 and Table 3 on pages 39-40.

Claim 142 finds support in the specification at Table 2 on pages 36-37 and Table 3 on pages 39-40. Claim 143 is supported by Formula I which discloses four nonconsecutive hydrophobic residues and Table 2 on pages 36-37 and Table 3 on pages 39-40. Note, an aliphatic residue is generally a hydrophobic residue. Claim 145 is supported, for example, by Formula I where a hydrophobic X_6 is interposed between hydrophobic X_5 and X_7; and by sequences disclosed on Table 2 on pages 36-37 and Table 3 on pages 39-40. Claim 146 is likewise supported, for example, by Formula I where hydrophobic X_6 and X_8 are interposed between X_5, X_7, and X_9 respectively; and by sequences disclosed on Table 2 on pages 36-37 and Table 3 on pages 39-40. Claim 148 is supported in the specification at page 31, line 20-page 32, line 5; and page 37, lines 2-12. Claims 149 and 150 are supported in the specification at page 32, lines 3-6; and page 37, lines 2-12. Claims 151-153 are supported in the specification at page 21, lines 21-25; page 32, lines 2-5; and page 37, lines 8-12; and page 48, lines 14-19. Claims 155 and 156 are supported by page 6, lines 14-17 and lines 23-26. Claim 157 is supported by the specification at page 48, lines 14-19.

I. REJECTION OF CLAIMS 1, 2, 4, 5, 8, 9, 13, 14, 16, 17, AND 19 UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Reconsideration is requested of the rejection of claims 1, 2, 4, 5, 8, 9, 13, 14, 16, 17, and 19 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Hydrophobic Amino Acid Residue Arrangement

On page three of the office action, the Office asserts that the phrase "at least two alternating hydrophobic amino acid residues" causes claim 1 to be vague and indefinite. Claim 1 has been amended to focus upon the peptide of Formula I and, thus, this rejection is now moot.

B. "Peptide Analog"

On page four of the office action, the Office asserts that the metes and bounds of what is meant by a peptide *analog*, as appearing in claim 1, are vague and indefinite. MPEP §2164.05(a) specifically dictates: "the specification need not disclose what is well known to those skilled in the art and preferably omits that which is well known to those skilled and already available to the public." Claim 1 has been amended to amplify the meaning of the original claim language.

As commonly understood in the art, a chemical *analog* refers to a molecule substantially similar in function to either the entire molecule or to a fragment thereof. It is also within the understanding of one skilled in the art that an analog may contain chemical moieties that are not normally a part of the molecule, but that may, for example, alter the molecule's binding affinity. Moieties capable of mediating such effects are disclosed in Remington's Pharmaceutical Sciences, 16th Ed., Mack Publishing Co., Easton, Pa., 1980. As such, a peptide analog would be commonly understood in the art to mean a molecule substantially similar in function to a peptide. For example, a peptide analog may have, for example, one or more substituted amide, or an isostere of amide, linkage(s) rather than amide linkages of a peptide. Or, in another example, a peptide analog could have bifunctional moieties bearing side-chain groups similar in structure to the side chains of the amino acids of a peptide.

The Office asserts that *analog* is vague and indefinite because "any change, addition, or deletion from some starting peptide could result in any resulting moiety of any length or composition." However, throughout the claims and specification, both peptide and peptide analog are used in the context of a corresponding number of residues. For example:

> Alternatively, the peptide or *peptide analog* may include a core sequence of, for example 10 residues, some of which are, for example, derived from PapA and the rest of which are, for example, derived from FimA.[4]
>
> [F]or describing the various peptide and peptide analog compounds, the amino acids can be conveniently classified into two main categories--hydrophilic and hydrophobic.[5]
>
> [S]uch peptides and peptide analogs will typically comprise at least two alternating hydrophobic amino acids.[6]

In analyzing amended claim 1 in light of the specification usage, it is clear that claim 1 describes Z_2 as an optional 1 to 5 residue peptide or a 1 to 5 residue peptide analog or some combination thereof. That is to say, the 1 to 5 residues could be peptide residues or peptide analog residues or a mixture of peptide residues and peptide analog residues. As such, the metes and bounds of said analog is clear. This interpretation is strengthened by the following passages:

> It is to be understood, however, that formula (I) includes *peptide analogs* in which one or more amide linkages is optionally replaced with a *linkage other than amide linkage*, preferably a substituted amide or an isostere of amide linkage. Thus, while the various X_n residues within formula (I) may conveniently be described in terms of "amino acids" or "residue," those having skill in the art will recognize that in embodiments having non-amide linkages, the term "amino acid" or "residue" as used herein refers to *other bifunctional moieties bearing side-chain groups similar in structure to the side chains of the amino acids.*[7]
>
> Compounds comprising formula (I) that are peptide analogs may provide significant therapeutic advantages, as their non-peptide interlinkages may confer the compound with enhanced stability towards proteases and/or peptidases, thereby conferring the compounds with increases *in vivo* stability compared to a corresponding peptide.[8]

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[4] Specification, p. 32, ln. 15-18.
[5] Specification, p. 15, ln. 11-13.
[6] Specification, p. 31, ln. 25-26.
[7] Specification, p. 33, ln. 10-17.
[8] Specification, p. 34, ln. 12-15.

> Peptide analogs typically contain at least one modified interlinkage, such as a substituted amide or an isostere of an amide....[9]

Thus, given the claim language, the consistent use of *peptide analogs* throughout the claims, and the common understanding of the term *analog* in the art, the metes and bounds of *peptide analog* as appearing in claim 1 is neither vague nor indefinite. These same arguments apply equally to claims 5, 9, and 16, and other such claims depending on claim 1. This argument also applies to claims 155 and 156 to the extent these claims employ the term analog.

C. "The Mimic of Claim 4"

On page four of the office action, the Office asserts that the phrase "The mimic of claim 4" makes claim 7 vague and indefinite as to whether only the mimic of claim 4 is intended or, alternatively, whether the subject of claim 7 is the compound of claim 4 but only with limiting mimic characteristics therein. Claim 7 has been cancelled. Note that the subject matter of claim 7, *i.e.* antibacterial activity against a group of Gram negative bacteria, has been retained in amended claim 19.

D. "Antibacterial Compound"

On page five of the office action, the Office asserts that "antibacterial compound" as appearing in claim 16 lacks a clear antecedent basis. Claim 16 has been redrafted as an independent claim. It is noted that claim 16 contains the requirement that the compound "inhibits pilus assembly." As disclosed by the specification, antibacterial activity includes inhibition of pilus binding[10] and, hence, inhibition of pilus assembly.

E. "Further Comprises"

On page five of the office action, the Office asserts that "further comprising" as it appears in claims 13 and 17 is vague and indefinite. Claim 13 and 17 have been amended to amplify that the claims are further conditions of specific residues of the claim upon which they depend. This was the original intention of the claim and, as

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[9] Specification, p. 34, ln. 23-24.
[10] Specification, p. 20, ln. 23-25.

such, the scope of the claims have not been altered. The listed group in claim 13 employs the same X_n terminology employed in claim 12 upon which it depends. Further, the "n" designations are not unique to claim 13. That is to say, claim 13 lists specific features of residues including X_1-X_5, X_7, X_8, and X_{10}, where these same designated residues appear in claim 12. Further, the claims and specification consistently use the X_n terminology throughout the application to refer to a specific peptide "sequence defined by residues X_1 through X_{10}."[11] The specification further lends credence to this interpretation in a detailed description of an embodiment of claim 13:

> Preferred amongst the 10 to 20 residue peptides and/or peptide analogs comprising formula (I) are those compounds having one or more of the following characteristics: X_3 is an aliphatic residue or T; X_5 is an aliphatic residue, F or G; and/or X_7 is G, N or A.[12]

Again, the listed positions are those specific residues of formula (I). Additionally, it is even more clear that this embodiment does not constitute added segments beyond the sequences of the claims (as the Office suggests), for the specification describes only selected sequences within formula (I) rather than reiterating the entire sequences.

As such, the amended claims and the specification clearly show that the X_n designated values of claim 13 and 17 match the correspondingly numbered specific residues of claim 1 and 16, respectively.

II. Rejection of Claims 6 and 10 under 35 U.S.C. § 112, First Paragraph

Reconsideration is requested of the rejection of claims 6 and 10 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. Claims 6 and 10 have been cancelled and the rejection is now moot.

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[11] Specification, p. 34, ln. 22; *see e.g.* p. 32, ln. 21; p. 34, ln. 16.
[12] Specification, p. 35, ln. 16-20.

III. REJECTION OF CLAIMS UNDER 35 U.S.C. §102(b)

Reconsideration is requested of the rejection of claims 1, 2, 4, 5, 8, 9, 16, and 19 under 35 U.S.C. §102(b) as being anticipated by Flemmer et al. and Kuehn et al. As held by the Federal Circuit, anticipation "requires identity of invention: the claimed invention, as described in appropriately construed claims, must be the same as that of the reference, in order to anticipate." *Glaverbel S.A. v. Northlake Mkt'g. & Supply, Inc.*, 45 F.3d 1550, 1554 (Fed. Cir., 1995). Thus, a claim is unpatentable by reason of anticipation only if "each and every limitation is found either expressly or inherently in a single prior art reference." *Celeritas Technologies, Ltd. v. Rockwell Intern. Corp.*, 150 F.3d 1354, 1361 (Fed. Cir., 1998).

A. Flemmer et al Does not Anticipate Claims 1, 2, 4, 5, 8, 9, 16, and 19

On page seven of the office action, the Office asserts that Flemmer et al. (1995, Bioorganic & Medicinal Chemistry Letters 5: 927-932) discloses a 19mer papG pilus C-terminal subunit peptide segment for inhibiting bacterial chaperone papD, and thus anticipates independent claim 1 and dependent claims 2, 4, 5, 8, 9, 16, and 19.

1. Construing Claim 1

The Office asserts that claim 1 includes Flemmer et al.'s 19mer C-terminal subunit peptide because the limitation of lines 2-3 are directed to a mimic of an amino *acid* motif of a pilus subunit.[13] Claim 1 reads, in pertinent part, a "mimic of an amino terminal motif of a pilus subunit," and not an amino acid motif.

On the basis of the broad definition of mimic, the Office asserts that a mimic requires only binding to a chaperone or another pilus subunit. The specification describes "a mimic of a pilus subunit" as "a substance which mimics (with respect to binding characteristics) an effective part of a pilus subunit."[14] Claim 1 specifies a "mimic of an amino terminal motif of a pilus subunit," and not a generic mimic of a pilus subunit as the Office suggests. Thus the *effective part* alluded to in the generic definition is, in the case of Claim 1, the amino terminal motif. This interpretation is supported by the

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[13] Office Action, ¶ 17, ln. 10.

provision of an example in the definition: "an effective part of a pilus subunit (e.g. the amino terminal portion of the pilus subunit)."[15] Thus, **an amino terminus mimic in the context of Claim 1 must mimic the binding characteristics of the amino terminal motif (*i.e.*, the effective part) of a pilus subunit**. Likewise, a chaperone G1 beta-strand mimic in the context of claim 1 must mimic the binding characteristics of the G1 beta-strand (*i.e.*, the effective part) of a chaperone.

2. The Flemmer 19mer does not mimic the binding characteristics of either the chaperone G1-β strand or the amino-terminal motif of a pilus subunit

In brief, Flemmer et al. describes a 19mer polypeptide that inhibits pilus assembly by binding to the G1-β strand of chaperone PapD. In contrast, the compounds of the invention inhibit pilus assembly by mimicry of the binding characteristics of either the chaperone G1-β strand or the amino-terminal motif of a pilus subunit. Both the chaperone G1-β strand and the amino-terminal motif of a pilus subunit bind to the hydrophobic core of a pilus subunit, for example PapK. To be a mimic in the context of claim 1 (*see* discussion *supra*), the 19mer should bind the hydrophobic pilus subunit core so as to inhibit pilus assembly. But, Flemmer et al.'s 19mer binds directly to the G1-β strand and as such does not mimic the G1-β strand. Because the 19mer does not bind the hydrophobic core of the pilus subunit in the manner of the chaperone G1-β strand or the amino-terminal motif of a pilus subunit, Flemmer et al.'s 19mer is not a mimic in the context of claim 1. A more detailed discussion of this argument follows.

As disclosed in the specification, the amino terminal motif of the PapK pilus subunit (or the chaperone G1 beta-strand) binds to the hydrophobic groove of an adjacent pilus subunit through the "donor strand complementation" mechanism.[16] Thus, **the amino terminus of PapK does not bind to the chaperone G1 β-strand**. Rather, they are analogous structures—the amino-terminus of the PapK pilus subunit *displaces*

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[14] Specification, p. 22, ln. 2-3.
[15] Specification, p. 22, ln. 3-4.
[16] *See* Specification, p. 23-26.

the G1 β-strand of the PapD chaperone and subsequently occupies the subunit groove previously occupied by the G1 beta-strand, in a mechanism termed "donor strand exchange."[17] Note, the hydrophobic groove of PapK is in fact composed, in part, of the carboxy-terminal F-strand of PapK.[18]

In contrast, Flemmer et al. discloses that the 19mer ionically bonds to the Arg^{8} and Lys^{112} of the G1-β strand of PapD.[19] Flemmer et al. suggests that the "model for binding of [19mer] polypeptides to PapD is based on critical anchoring of the C-terminal carboxylate group of the [19mer] peptide to PapD, followed by 'zippering' of the [19mer] peptide to PapD by hydrophobic interactions and hydrogen bonds."[20] Thus, in Flemmer et al., **the 19mer does not mimic the binding characteristics of the G1-β strand of PapD or the amino-terminus of PapK** because the 19mer directly binds the G1-β strand of PapD and not the hydrophobic groove (*i.e.*, the carboxy terminal F-strand) of PapK.

As discussed above, the amino terminus of PapK does not bind the G1-β strand of PapD; on the contrary, it competes for the same binding site in the hydrophobic groove of another pilus subunit. Because the Flemmer et al. 19mer inhibits pilus assembly via directly binding the G1-β strand of PapD and does not interact directly with the hydrophobic groove of PapK, it is not a mimic of a chaperone G_1 beta-strand or an amino terminal motif of a pilus subunit in the context of claim 1.

As an example of another pilus subunit, it is known in the art that the amino terminal motif of PapG (a pilus subunit) binds to a Galα(1-4)Gal disaccharide moiety.[21] As Flemmer et al.'s 19mer does not bind to this disaccharide moiety, the 19mer does not mimic the amino terminal motif of the PapG pilus subunit.

The preceding arguments apply equally to claims depending upon claim 1, which includes claims 2, 4, 5, 8, 9, 16, and 19.

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[17] Specification, p. 22, ln. 17-19; p. 26, ln. 16-18.
[18] Specification, p. 26, ln. 5-7.
[19] Flemmer et al, p. 928, ln. 4-5.
[20] Flemmer et al, p. 929, ln. 33-35.
[21] Flemmer, p. 929, ln. 11-12.

3. The 19mer peptide of Flemmer et al does not anticipate formula (I) of claims 1 and 12

On page seven of the office action, the Office asserts that the X and Z moieties of formula (I), as appearing in claims 1 and 12, are anticipated by the 19mer disclosed by Flemmer et al. Specifically, the Office states that Z_1-X_2, as appearing in claim 1 formula (I), is represented by Gly(19') to Ser(11') in the 19mer of Flemmer et al. The Office's analysis, however, relies upon calling a seven-peptide sequence within the Flemmer et al. 19mer (from Gly(19') to Glu(13')) a "peptide analog" as that term is allegedly used in claim 1 of the application. As discussed *supra*, this interpretation of "peptide analog" is erroneous. Rather, claim 1 describes Z_2 as an optional 1 to 5-residue peptide, a 1 to 5-residue peptide analog, or some combination thereof. As such, Flemmer at al's 7 residue sequence from Gly(19') to Ser(11') does not conform to a sequence limited to 5 residues. So, the 19mer polypeptide disclosed in Flemmer et al. does not contain "each and every limitation" possessed by claim 1. Thus, the 19mer polypeptide disclosed by Flemmer et al. does not anticipate formula (I) of claim 1 because all limitations of the invention are not present. The above argument applies equally to 2, 4, 5, 8, 9, and 19, as well as other claims dependent upon claim 1. The above argument also applies to claim 16 where Z_{12} corresponds to Z_2.

Also, the Office asserts that Thr(7') of the Flemmer et al. 19mer represents X_6, as appearing in claim 1, by virtue of threonine being a hydrophobic residue. It is noted that the specification classifies threonine as a hydrophilic amino acid and also a hydroxyl-substituted aliphatic amino acid, but not a hydrophobic residue.[22]

B. Kuehn et al Does Not Anticipate Claims 1, 2, 4, 5, 8, 9, 16, and 191

On page eight of the office action, the Office asserts that Kuehn et al. (1993, Science 262: 1234-1241) anticipated independent claim 1 and dependent claims 2, 4, 5, 8, 9, 16, and 19 under 35 U.S.C. §102(b).

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[22] Specification, p. 16, ln. 5; p. 17, ln. 14.

Kuehn et al. discloses the identical 19mer peptide sequence of the carboxy-terminus of PapG as disclosed in Flemmer et al.[23] As such, the arguments made *supra*, in connection with alleged anticipation by Flemmer et al., apply equally to the asserted anticipation by Kuehn et al. of claims 1, 2, 4, 5, 8, 9, 16, and 19.

Additionally, the Office asserts that a 16mer appearing in Kuehn et al. anticipates claim 1 with the Z_2 limitation being a 4 residue peptide. In amended claim 1, X_8 is limited to any amino acid other than an aliphatic residue (*i.e.*, not alanine, valine, leucine, or isoleucine). The 16mer of Kuehn et al. discloses valine (an aliphatic residue) in the X_8 position and so does not anticipate Formula I of claim 1.

As such, the sequences disclosed by Kuehn et al. do not anticipate Formula I of claim 1. The above argument applies equally to 1, 2, 4, 5, 8, 9, 16, and 19, as well as other claims dependent upon claim 1.

[23] Kuehn et al, p. 1235, Table 2.

IV. CONCLUSION

In light of the foregoing, Applicants request an entry of the specification amendment, claim amendments, and abstract amendments; request a withdrawal of claim rejections; and solicit allowance of the claims. The Office is invited to contact the undersigned attorney should any issue remain unsolved.

A check in the amount of $355.00 is enclosed ($145.00 for the addition of multiple dependent claims; and $210.00 to cover the two month extension of time). The Commissioner is hereby authorized to charge any underpayment and credit any overpayment of government fees to Deposit Account No. 19-1345.

Respectfully submitted,

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